NOVEMBER 1956

Disease-a-Month

Bacterial Endocarditis

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THE YEAR BOOK PUBLISHERS • INC.
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Bacterial Endocarditis

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BACTERIAL ENDOCARDITIS has undergone a significant evolution during the past decade, and a review of its present status seems appropriate. Of greatest interest is the dramatic change which has occurred in the general outlook with the availability of antibiotic therapy. A high proportion of cases can now be cured if they are recognized sufficiently early and treated promptly with the proper antibiotic or combination of antibiotics. The current bacteriologic, clinical and therapeutic status of bacterial endocarditis will be emphasized in this review. No attempt will be made to deal completely with the voluminous literature on this disease. Kerr (1) has recently published a monograph on subacute bacterial endocarditis

with 800 references which provides an excellent key to the literature. Classification of endocarditis in terms of the causative bacterial agent now appears to have great practical importance with the availability of specific therapy, and for this reason the subdivision of endocarditis into acute and subacute forms will not be emphasized here.

INCIDENCE

Bacterial endocarditis is not a reportable disease and, hence, no accurate figures exist on its incidence. It can be classed as a relatively uncommon disease in the general population, but by no means rare, in that it has been found in 1 to 2% of autopsies in several series. It is a fairly frequent event in patients with rheumatic heart disease, and up to approximately 25% of such patients have been estimated to develop bacterial implants sooner or later. A similar incidence has been found in patients with congenital heart lesions, notably interventricular septal defects, patent ductus arteriosus and bicuspid aortic valves. It is somewhat less common in coarctation of the aorta and is extremely rare in interatrial septal defects. Dowling and Murray (2), on the basis of the incidence of bacterial endocarditis in Washington, D. C. in 1948, estimated that if the same rate obtained elsewhere, there would have been a total of 3,400 cases of this disease in the United States in that one year.

The widespread use of antibiotics apparently has resulted in a slightly decreased incidence in recent years. Littmann and Schaaf (3) reported the incidence per thousand admissions to three Boston hospitals to be 1.12 and 0.59 for the periods 1944-46 and 1947-49 respectively. Autopsy data reveal a similar trend. Angrist and Marquiss (4) in New York observed endocarditis to account for 1.85% of autopsies during the years 1936–46 as compared to 0.47% for the period 1946–51.

Although the disease may be seen at any age, the peak incidence occurs in the third and fourth decades. It is rare before the age of ten. Either sex may develop the condition, males being affected slightly more frequently than females in most reported series.

BACTERIOLOGY

The bacteriology of endocarditis has been altered to some degree during the past antibiotic decade. Some organisms noted for their drug resistance, such as staphylococci, enterococci and certain gram-negative bacilli, are encountered more frequently at present, and their relative importance in this disease appears to be increasing. Other organisms outstanding for their drug sensitivity, especially pneumococci, gonococci and beta hemolytic streptococci, are now rarely seen in comparison to their relative prominence ten to twenty years ago.

Isolation and identification of the causative agent have always been required for a certain diagnosis of bacterial endocarditis, and this procedure has now become a matter of urgent practical concern with specific antibiotic therapy potentially available for every case. Successful therapy basically hinges on knowing what micro-organism is responsible for the endocardial infection at hand. A bacteriologic diagnosis can be made in between 70 and 90% of patients and is not a major task in most instances (1). The organisms usually encountered are hardy and can be isolated with comparative ease. Their proper identification is not a major problem, providing certain basic facts are kept in mind.

Non-hemolytic Streptococci (Viridans Streptococci and Enterococci)

Viridans streptococci are still the most frequent cause of bacterial endocarditis and account for anywhere from 75 to 85% of cases. They are almost invariably associated with endocarditis running a course of several weeks or months in duration. The viridans streptococci are a major part of the normal flora of the upper respiratory tract and have little propensity to cause disease other than endocarditis. They comprise a heterogeneous group of micro-organisms whose classification is at present unsatisfactory. Although several varieties are recognized, no one is primarily prone to cause endocarditis and, thus, individual strains need be identified

only as belonging to the viridans streptococcal group. It should be emphasized that these organisms exhibit variable hemolytic activity on blood agar, depending on the species of blood employed and the strain in question. Classically, they produce "greening" or alpha hemolysis on blood agar and for this reason are often referred to as the "green streptococci." This terminology is somewhat misleading, however, since at least one variety encountered frequently in endocardial infections gives no hemolytic reaction whatsoever on blood agar. None of these organisms causes complete or beta hemolysis on blood agar, and in this respect they can be distinguished readily from group A hemolytic streptococci. The antibiotic sensitivity of viridans streptococci has not changed materially in recent years. More than 75% of strains are penicillin sensitive, being inhibited in vitro by 0.02 to 0.1 units/ml. of penicillin. Berntsen (5) found no apparent tendency for strains to become penicillin resistant during a 10 year period of extensive use of this drug in the general population. Approximately 50% of strains are streptomycin sensitive, and the majority of strains are inhibited by the broad spectrum antibiotics.

Enterococci are responsible for 5 to 15% of cases of endocarditis, and the experience in several clinics suggests that they are encountered more frequently now than several years ago. These organisms are also primarily associated with endocarditis having a subacute course. Enterococci are part of the normal intestinal flora and occasionally can be isolated from the mouth and vagina. All elaborate a specific somatic C carbohydrate and are classified as group D streptococci by the Lancefield technic. Again, several varieties are recognized, but for practical purposes individual strains need be identified only as enterococci. *It is crucial that enterococci be clearly distinguished from viridans streptococci since they require special and materially different therapy.* Certain characteristics of enterococci permit this differentiation to be made without elaborate studies. First of all, they grow over a temperature range of 10 to 45 C. Secondly, growth occurs in media containing 0.1% methylene blue, 40% bile or 6.5% sodium chloride. It should be stressed that enterococci may

show considerable variation in their hemolytic activity on blood agar. Individual strains may show "greening" or no hemolytic activity and in this respect can be confused with viridans streptococci if further tests are not carried out. Some enterococci produce true beta hemolysis on blood agar and may be confused with group A hemolytic streptococci. The enterococci are more pathogenic than viridans streptococci and from time to time cause peritonitis and genitourinary tract infections in addition to endocarditis. They also have a tendency to cause abscesses in various organs, particularly the spleen.

Of great importance is the fact that essentially all strains of enterococci are penicillin resistant and usually require 1.5 to more than 25 units/ml. of penicillin for inhibition of growth in vitro. This characteristic penicillin resistance is useful as a practical aid in the identification of enterococcal strains. These organisms are also usually resistant to streptomycin in vitro. In contrast, most strains may be expected to be sensitive to erythromycin, chloramphenicol and the tetracyclines in the amounts usually employed for sensitivity testing. At face value, therefore, one would anticipate that penicillin and streptomycin would have little use in the therapy of enterococcal endocarditis and that erythromycin or one of the broad spectrum antibiotics would be the drug of choice. This is *not* the case, however. As will be discussed later, the combination of penicillin and streptomycin exerts a dramatic "killing" effect on enterococci in vitro, and this drug combination has proven superior to any other program devised thus far for enterococcal infections.

Staphylococci

The position of staphylococci with respect to endocarditis has assumed increasing importance in recent years. Strains encountered at present are frequently resistant to one or more antibiotics, and the proportion of cases of endocarditis due to staphylococci appears to be increasing. Staphylococci are usually associated with forms of endocarditis running a rapid and fulminating course but may cause infections whose

clinical course is indistinguishable from streptococcal subacute bacterial endocarditis. It is estimated that these organisms are responsible for about 10% of all forms of endocarditis; that is, both the acute and subacute varieties.

Staphylococcus aureus and Staph. albus (Micrococcus pyogenes var. aureus and M. pyogenes var. albus, respectively) are the two varieties of importance. Both are found on the skin and among the normal flora of the upper respiratory tract. The great capacity of staphylococci to invade tissues and their propensity for abscess formation are well known. Pathogenicity is usually, but not invariably, associated with coagulase production and hemolytic activity on blood agar. The albus variety should not be regarded as a harmless saprophyte since it is an important cause of endocarditis, as emphasized in the recent review of staphylococcal endocarditis by Dowling and his associates (6).

The increasing prevalence of antibiotic-resistant staphylococci has attracted world-wide attention. The percentage of drug-resistant strains in a given location can usually be directly correlated with the extensive use of an antibiotic in that area. When penicillin first became available, essentially all strains were sensitive to this antibiotic. In contrast, more than 50% of strains are now penicillin resistant, and many strains are resistant to one or more of the tetracycline antibiotics as well. Erythromycin, chloramphenicol and bacitracin have not been used as extensively as the other antibiotics, and most strains of staphylococci are still sensitive to these agents. The point to be emphasized is that different strains of staphylococci show tremendous variability with respect to their antibiotic sensitivity patterns. One cannot predict what type of pattern a given isolate will exhibit, and for this reason each staphylococcus must be handled as an individual problem and be subjected to detailed in vitro study.

Other Organisms

Pneumococci still cause acute types of endocarditis, but the frequency of encountering this organism in endocarditis has decreased during the past decade. Pneumococci cause "green-

ing" on blood agar and therefore may be confused with viridans streptococci and enterococci, but their bile solubility and reaction on inulin usually permit them to be distinguished without difficulty from these other organisms. All strains are still exquisitely sensitive to penicillin as well as to other antibiotics, and drug resistance is not a problem.

Many other organisms have the capacity to cause endocarditis but do so very rarely. Certain gram-negative rods such as Klebsiella and Pseudomonas species are encountered somewhat more often now and pose serious problems because of their resistance to most antibiotics. Individual study of each strain is essential in planning antibiotic therapy, and the use of agents such as polymyxin, neomycin or other newer antibiotics must be considered.

ANTIBIOTIC SENSITIVITY TESTS

Antibiotic sensitivity tests have clearly proved a great aid in the selection of drugs for treating endocarditis. However, certain limitations inherent in these tests as performed in most laboratories should constantly be kept in mind.

First of all, the usual in vitro technic tells one only what concentration of a drug prevents visible growth of an inoculum either in tubes or on agar plates. The end-point is inhibition of growth. No information is obtained concerning the amount of drug required to give a bactericidal effect or to kill the organism in question, and *it is this point which appears crucial for effective therapy.* For example, an enterococcus may be reported as highly sensitive to a tetracycline drug but resistant to penicillin and to streptomycin. Yet in most cases tetracycline will not kill a population of enterococci and will not cure the infection, whereas the combination of penicillin and streptomycin will usually do both.

Second, antibiotic sensitivity tests always provide optimal conditions for the interaction of drug and organism. The conditions which obtain in vivo are quite different. Fibrin and tissue debris have to be penetrated by an antibiotic before it can finally make contact with the bacteria and, even after arriving at the bacterial nidus, local factors such as pH and

the metabolic state of the bacteria may have an untoward effect on the final effect the drug is able to exert. Eagle (7) has clearly demonstrated the problem of eradicating organisms which are no longer multiplying and metabolizing at a rapid rate in mice infected with group A hemolytic strepto-

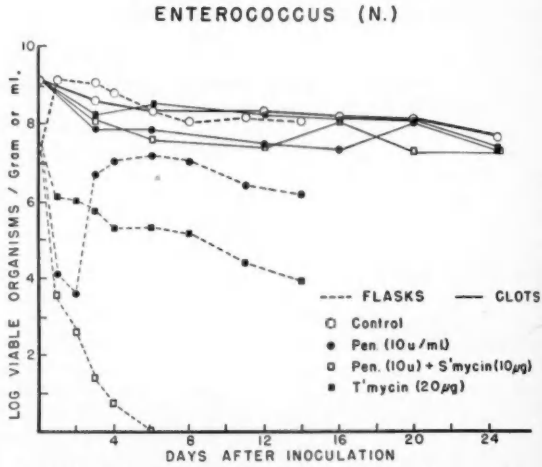

FIG. 1.—Effect of penicillin alone, penicillin combined with streptomycin and terramycin® alone on enterococcus, strain N.

cocci and subsequently treated with penicillin. Such factors as these provide an explanation as to why in vitro antibiotic sensitivity tests may on occasion fail to correlate with in vivo antibiotic therapy.

Third, antibiotic sensitivity tests are usually set up with different drugs tested individually against a given bacterial inoculum, and thus no information is furnished as to the effect of drug combinations on the organisms. It is well established that combinations of drugs may exert synergistic or antagonistic effects on organisms under certain well-defined experimental conditions (see Treatment, p. 34).

A series of in vitro experiments carried out by one of the authors (THH) a few years ago indicated that the combination of penicillin and streptomycin possessed a synergistic and bactericidal effect against enterococci and some strains of viridans streptococci (8, 9, 10). This combination of antibiotics was found to provide a bactericidal effect against these organisms which could either not be realized at all with either drug alone or which occurred more rapidly when the drugs were used together. In these experiments a known number of organisms was inoculated into nutrient broth in flasks and/or into human blood which, after forming a clot, was suspended in tubes containing broth. Antibiotics were added at the time of inoculation to all flasks or tubes containing blood clots, except the controls, to give known concentrations, and daily thereafter to restore the antibiotic levels approximately to their original values. At intervals the number of viable organisms remaining in the flasks or suspended blood clots was determined by a quantitative technic. Penicillinase was added whenever 0.01 unit/ml. or more of penicillin was present.

The effects of penicillin alone, penicillin and streptomycin in combination and terramycin on a strain of enterococcus isolated from a patient with endocarditis are shown in Figure 1.

In the portion of this experiment employing flasks, it will be noted that "killing" of this organism occurred only with a combination of penicillin and streptomycin. Penicillin alone reduced the number of bacteria temporarily but failed to sterilize the culture medium. Terramycin® also failed to eradicate the inoculum. Yet on the basis of in vitro antibiotic tests, terramycin® appeared to be the drug of choice for therapy of this patient since the organism was sensitive to this antibiotic and resistant to penicillin and streptomycin. The protective effect provided by the blood clots for these organisms is also well demonstrated here. Organisms remained viable for as long as four weeks in the clots in spite of a penicillin-streptomycin environment. The patient from whom this organism was recovered was cured by a six weeks' course of penicillin and streptomycin, however, which suggests that

enterococci can be eradicated from vegetations in vivo with greater ease than in clots in vitro under the conditions of this experiment, but that prolonged therapy is required.

The effects of penicillin alone and combined with streptomycin against a strain of viridans streptococcus are shown in Figure 2.

This organism was recovered from a patient with endo-

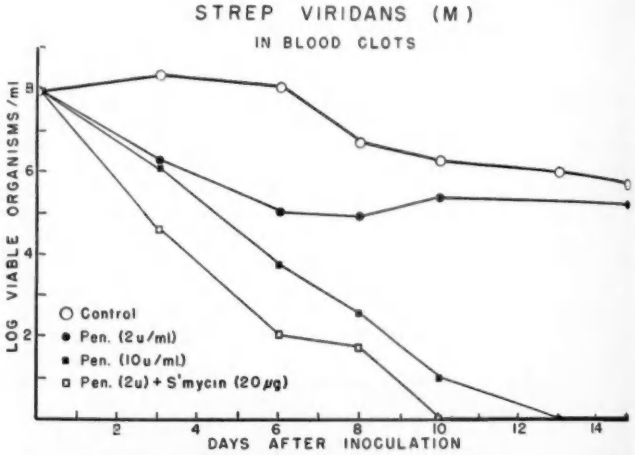

FIG. 2.—Effect of penicillin alone and penicillin combined with streptomycin on viridans streptococcus, strain M.

carditis and was inhibited by 0.1 unit/ml. of penicillin or less in the routine tube dilution sensitivity test. Penicillin alone in amounts of 2 units/ml. failed to eradicate this organism in blood clots, illustrating the discrepancy which often can exist between bacteriostatic and bactericidal concentrations of penicillin for a given organism under varying conditions. One hundred times the inhibitory concentration of penicillin did produce a bactericidal effect and rendered the clots sterile in 13 days. The lower concentration of peni-

cillin combined with streptomycin exerted a more rapid bactericidal action and sterilized the clots within 10 days.

These observations indicate that penicillin-streptomycin combinations can "kill" enterococci and probably accelerate the eradication of viridans streptococci, at least under the conditions described. Such in vitro studies provide a rational basis for the selection of antibiotics for the treatment of this disease and have correlated well with clinical therapeutic results over the years.

PATHOGENESIS

Despite certain gaps in existing knowledge, the basic pathogenesis of endocarditis may be stated to consist of two crucial events. The first is *bacteremia* which permits bacteria to enter the blood stream and come in contact with cardiac structures. The second is the *implantation of bacteria on cardiac endothelium*.

Bacteremia

Bacteremia of a transitory and asymptomatic nature is probably a fairly frequent accompaniment of day-to-day living and presumably occurs from time to time with such events as chewing and brushing the teeth. Bacteremia may, therefore, be relatively "silent," and this explains why no portal of entry can be found in at least one third of the cases of endocarditis. In contrast, viridans streptococci and enterococci are known to invade the blood stream frequently in association with certain procedures such as tooth extraction, tonsillectomy and urinary tract manipulation, and these procedures are often directly implicated in the development of endocardial infection. Viridans streptococci can be recovered from the blood immediately after dental extraction in between 10 and 83% of cases, the incidence varying with the extent of oral infection, the number of teeth extracted and the degree of trauma involved. A dental focus was believed to be responsible for about 50% of the cases of endocarditis studied by Cates and Christie (11). Bacteremia has been demonstrated to occur

following tonsillectomy and urinary tract instrumentation in 10 to 40% of cases. Viridans streptococci are the common agents isolated from the blood after tonsillectomy, whereas enterococci, staphylococci and gram-negative rods predominate following urinary tract manipulation. Prostatectomy has received special attention as a potential cause of enterococcal endocarditis and has been the subject of at least two reports in recent years.

A variety of other procedures such as incision and drainage of furuncles, normal delivery, abdominal operations and even bronchoscopy and sigmoidoscopy have been either directly or indirectly implicated in the production of bacteremia and may under certain circumstances lead to bacterial endocarditis.

Staphylococcal or pneumococcal bacteremia is usually secondary to some recognizable primary infection with these agents. Staphylococcal bacteremia may result from many causes, particularly skin lesions and pulmonary and genitourinary tract infections, or may be an important complication of heroin and morphine addiction of the "main liner" type as pointed out by Dowling and his co-workers (6). Pneumococcal pneumonia results in bacteremia in at least one third of the cases and still represents the most important cause of pneumococcal endocarditis.

Implantation of Bacteria on Cardiac Endothelium

A wealth of data supports the concept that bacteria become implanted on cardiac endothelium directly from the blood stream. It is clear that some of the more pathogenic organisms, notably staphylococci and pneumococci, may on occasion infect what appear to be normal heart valves. These organisms are apt to be encountered in patients who give no past history of cardiac disease and who show no objective evidence of cardiac abnormalities during the initial phases of their illness. The pathogenicity and virulence of these pyogenic cocci is reflected not only by their capacity to infect

essentially normal valves but by the acute and fulminating nature of the endocardial infection they precipitate.

In most cases, however, some basic underlying cardiac abnormality accounts for bacterial implantation, and this is essentially always the case with viridans streptococcal endocardial infections. The underlying abnormality is usually a damaged aortic valve or insufficient mitral valve resulting from prior rheumatic fever, and between 85 and 90% of patients with non-hemolytic streptococcal endocarditis are found to have rheumatic heart disease (11). Congenital cardiac abnormalities, notably interventricular septal defects, patent ductus arteriosus and bicuspid aortic valves, are encountered next in frequency. Luetic valvular disease rarely is associated with bacterial implants, probably because the primary damage here is to the aortic ring and not to the valves themselves.

In the final analysis these conditions are characterized by altered circulatory dynamics which result in abnormal pressure gradients being brought to bear upon a valve or some area of cardiac endothelium. The end-result is endothelial injury. The importance of increased cardiac work with its attendant stress and strain on cardiac endothelium has been well illustrated by the studies of experimental endocarditis in animals carried out by Lillehei, Bobb and Visscher (12) and by Highman and Altland (13). These investigators found that dogs prepared with large arteriovenous fistulas or rats placed at simulated high altitudes often developed bacterial valvular vegetations either spontaneously or following intravenous injection of bacteria. Those valves exposed to the greatest pressure gradients during normal life would be expected to suffer most injury from continued stress and strain, and this thesis may explain why bacterial endocarditis in more than 90% of cases affects the left side of the heart.

Endothelial injury, regardless of whether it results from rheumatic fever or from abnormal pressure gradients associated with congenital defects or from other unknown causes, almost invariably results in the formation of platelet thrombi and/or degeneration of subintimal collagenous tissue. These morphologic abnormalities probably provide the critical fer-

tile soil for implantation and propagation of bacteria arriving by way of the blood stream. Grant, Wood and Jones (14), Keefer (15) and Allen and Sirota (16) have emphasized the crucial role of platelet thrombi and subintimal collagenous alterations (nonbacterial thrombotic endocarditis) in the pathogenesis of endocarditis, and this view would appear to be supported by all data at the present time. Indeed, platelet thrombi may accumulate to a considerable extent and embolize without bacterial infection ever occurring, thereby producing a clinical entity which may simulate bacterial endocarditis in many respects.

PATHOLOGY

Since bacterial endocarditis is essentially an intravascular infection characterized by bacteremia and embolic phenomena, the pathologic manifestations of this disease may be observed in a variety of organs in addition to the heart.

Heart

Vegetations occur most frequently on the mitral valve. This valve was involved either singly or in combination with other valves in approximately 75% of the cases reported by Cates and Christie (11). Aortic valve vegetations are observed somewhat less often but deserve special emphasis because of the unfavorable effect they exert on the course of this disease. Damage to the aortic valve from eroding vegetations frequently aggravates pre-existing valvular incompetence and not infrequently culminates in perforation or rupture of one or more valve leaflets with rapid death. Tricuspid or pulmonary valve involvement occurs in less than 10% of cases and is most apt to be seen in association with staphylococcal or other pyogenic coccal infections.

Vegetations are most prone to occur on the free margins of the valves, especially on the contact surfaces, but they often extend to involve the ascending aorta, adjacent mural endocardium, chordae tendineae or papillary muscles. In congenital heart conditions the implants are seen in the anatomic

defect itself, along adjacent endocardium in the direction of maximal blood flow or on opposing endothelial surfaces at some distance from the congenital lesion. Most vegetations are fairly soft and friable and hence readily shed fragments into the circulation with consequent embolization of many organs. They may vary in size from inconspicuous and scattered implants to huge fungating masses which practically occlude the entire orifice of a valve.

The microscopic features of well-developed vegetations have been studied in detail by Moore (17). A large central necrotic core of acellular debris makes up 75% or more of the total bulk of the lesion. Adjacent to this necrotic nidus lie the colonies of bacteria which in turn have a peripheral and superficial acellular covering composed primarily of fibrin. The necrotic core of bacterial vegetations appears to be identical to the necrotic center characterizing the verrucae of rheumatic origin and the non-bacterial thrombotic verrucae which can be found on any damaged cardiac endothelium. Angrist and Marquiss (4) have noted that uninfected thrombi composed of platelets and amorphous material are frequently seen in proximity to the mature bacterial vegetations.

Moore (17) has noted some evidence of healing in all vegetations regardless of whether or not antibiotics have been administered, although, as expected, healing progresses at a much faster rate and is more advanced under the influence of specific therapy. The exposed surface of the vegetation is first covered with fibrous tissue. Granulation tissue then invades the layer of bacterial colonies, providing a framework for polymorphonuclear leukocytes which subsequently begin to move in and make contact with the bacteria. Phagocytosis occurs at a painfully slow rate and is accompanied in time by calcification of the bacterial mass. Subsequently the necrotic core undergoes hyalinization and calcification which, incidentally, causes further damage to the valve and probably contributes materially to the development of heart failure in this disease. The end-stage of healing consists of endothelialization of the spaces created in the vegetation by the ingrowth of granulation tissue and the migration of poly-

morphonuclear leukocytes. The healing process is slow and requires three to six months for its completion. During this interval sterile fragments often break off, causing embolic lesions, and such occurrences cannot be taken as ipso facto evidence of relapse.

Bacteria can be seen in stained sections of vegetations in more than 50% of patients dying late in the course of their disease after what would appear to have been a cure of their infection by all clinical criteria (11). These bacteria usually cannot be cultured in vitro, and whether they represent dead or viable organisms remains a question. It is possible that organisms are still viable although rendered incapable of growth in vitro because of their exposure to antibiotics in the patient. The point to be emphasized is that bacteria can be seen in vegetations late in the course of this disease and thus represent a potential cause of relapse if treatment is not vigorous and carried on for a sufficient period.

Sheldon and Golden (18) have recently emphasized the occurrence of single or multiple abscesses of the valve rings of the heart in cases of staphylococcal or pneumococcal endocarditis. Their presence can be recognized grossly by swelling in the region of the valve rings and/or by crater-like openings in adjacent mural endocardium or sinuses of Valsalva which represent points of rupture. The lesions vary from one to several centimeters in size and consist of a necrotic and suppurative center surrounded by granulation tissue. Although valve ring abscesses cannot be diagnosed with certainty clinically, they should be suspected in patients with pyogenic coccal endocardial infections and may be a cause of continuing sepsis and lead to progressive cardiac failure.

Myocardial changes, which can be found in the majority of fatal cases of endocarditis, represent another factor in the production of heart failure. Focal or diffuse areas of myocarditis are observed most often and consist of perivascular accumulations of polymorphonuclear leukocytes, mononuclear cells and fibroblasts without appreciable necrosis. Such lesions are believed to originate from direct seeding of the myocardium with bacteria or from an allergic response of vessels to bacteria and their products. Indeed, similar vascu-

lar lesions may be seen in many organs. Single or multiple foci of necrosis may occur in random fashion within the myocardial tissue from microembolization and have the character of abscesses or infarcts, depending on whether the responsible emboli are septic or bland in nature. Although coronary emboli infrequently cause clinical manifestations of frank myocardial infarction, subclinical embolization with the production of microscopic infarcts is a common event and can be recognized in up to 40% of cases coming to autopsy (19). Concurrent active rheumatic fever probably occurs in less than 10% of cases and consequently Aschoff nodules are not commonly encountered.

Embolization and Mycotic Aneurysms

Embolization occurs in practically all cases of bacterial endocarditis of any standing. Consequently infarcts of varying size can usually be found in many organs at autopsy, notably the spleen and kidneys. These infarcts more often than not are caused by bland emboli and do not have a suppurative character. The origin of such bland emboli is not always clear, but presumably they arise either from superficial bacteria-free portions of the vegetations or from non-bacterial thrombotic deposits adjacent to the bacterial implants. Septic emboli pose more serious problems because of their capacity to induce inflammatory changes wherever they come to rest. Disseminated abscesses are the rule in staphylococcal endocarditis and contribute materially to the septic and fulminant nature of this type of infection.

Emboli laden with bacteria may also set up infection in the wall of small or large arteries and result in the production of mycotic aneurysms. The pathogenesis of mycotic aneurysms differs, depending on the size of the vessel involved. Aneurysms affecting the base of the aorta or pulmonary artery originate by direct extension of bacterial vegetations on the aortic or pulmonary valve respectively. Other portions of the aorta or relatively large arteries develop aneurysmal dilatations as a result of septic emboli entering the vasa

vasorum and coming to lodge within the deeper portions of the arterial wall.

Mycotic aneurysms more commonly develop in the smaller arteries of the internal organs or extremities and arise anatomically in situations where emboli are most likely to stick; namely, the bifurcation of arteries or places where vessels turn sharply or undergo a sudden constriction. Aneurysmal dilatation results from the destructive nature of the local vascular inflammatory process.

Mycotic lesions usually range from a few millimeters to several centimeters in size and can be easily overlooked. The histologic features of these lesions consist of loss of the intima, destruction of the elastic tissues and inflammatory changes within and adjacent to the vessel ranging from diffuse infiltration of leukocytes to actual micro-abscess formation. Bacteria may be seen on section or cultured from the lesion. Mycotic aneurysms are prone to rupture wherever they arise, and this event is usually fatal if it occurs in a vital area such as the brain or involves a large vessel such as the aorta, with massive bleeding. In contrast, aneurysms of the peripheral arteries, surrounded by muscle tissue and fascia, are less prone to give rise to free bleeding but, rather, enlarge slowly and rupture with formation of a false aneurysmal sac with a wall composed of laminated blood clots and tightly compressed adjacent tissues.

Spleen

The spleen is the most common site of embolization, and the frequent occurrence of infarction in this organ readily explains why it is so often palpable in this disease (1). Septic emboli or circulating bacteria lodging in this organ may elicit suppuration with the formation of abscesses. These splenic abscesses are difficult to sterilize, and they may be the cause of persistent bacteremia and continuing sepsis despite therapy. In such cases, splenectomy may be required before the infection can be eradicated.

Kidney

Pathologic changes are commonly encountered in kidneys at autopsy (20), and the lesions are responsible for a fatal outcome in approximately 10% of cases (11). Abscesses and diffuse interstitial inflammatory changes are most apt to occur in staphylococcal endocarditis and can seriously compromise renal function. Embolic glomerulonephritis due to the lodging of minute emboli in glomerular capillaries is a frequent finding in non-hemolytic streptococcal infections. Isolated glomerular units are involved in random fashion, and hence this type of lesion does not ordinarily lead to renal failure. The most serious lesion consists of a diffuse type of glomerulonephritis characterized by proliferation of endothelial cells of the glomerular loop and accumulations of mononuclear cells. Epithelial crescents and thrombotic lesions of the afferent glomerular arterioles further complicate the picture. This process, usually associated with viridans streptococcal infections, is more apt to reach its full development relatively late in the course of endocarditis and is apparently uninfluenced by antibiotic therapy. From a morphologic standpoint it appears to be essentially identical with the diffuse glomerulonephritis following beta hemolytic streptococcal infections, and immunologic mechanisms have been considered important in its pathogenesis. Diffuse glomerulonephritis may be acute or subacute and variably reversible with the passage of time. On the other hand, this lesion can progress to a chronic stage with fibrosis and obliteration of great numbers of glomerular units and ultimately result in progressive renal decompensation and finally death.

CLINICAL FEATURES

General Picture

The clinical manifestations of bacterial endocarditis are extremely variable, and although the full-blown disease is readily recognized, it is unfortunately true that the diagnosis is usually not made until the infection has been present for

many weeks or months. Furthermore, patients all too frequently still come to autopsy before the presence of the disease is suspected. On the other hand, because of diagnostic difficulties, a number of patients are undoubtedly being treated for bacterial endocarditis who have some other cause of prolonged fever.

It is obvious that early diagnosis is of paramount importance if treatment is to be effective in eradicating the infection before irreparable damage has been done to heart valves and before major irreversible embolic lesions have occurred. The difficulties attending this problem become apparent when the vagaries and variability of all diagnostic criteria are considered.

In general, the findings in this malady can be divided into those arising from the underlying heart disease itself, those attributable to chronic sepsis and those related to embolic lesions. Hence the cardinal findings of a heart murmur, fever and emboli form the classical diagnostic features. Of these, the first two are almost always present at some stage, but clinically evident embolic manifestations tend to occur less regularly and often only late in the disease.

Onset

The onset is insidious in two thirds of cases, and in many of these it may be impossible to date the beginning of the infection with any accuracy at all (11). Patients often simply begin to feel below par and suffer mild fatigue, anorexia and weight loss. Then, perhaps only after several weeks, they discover fever or some other more tangible evidence of organic disease by which the probable onset can be dated. Most frequently, the patient is considered to have "flu" or "grippe" which fails to clear up, and sooner or later the true cause of the symptoms becomes apparent.

In the remaining group the onset is relatively abrupt and may occur in an endless variety of ways, most commonly with chills and fever. Sometimes the first symptom is hemiplegia, a shower of petechiae or some other embolic affair. Rarely, patients present with the picture of myocardial infarc-

tion which presumably is due to embolization of a coronary vessel.

The protean symptoms resulting from embolization of various organs are such that patients with bacterial endocarditis may appear in any specialty clinic, and unless the complete history and physical examination are attended to, the underlying diagnosis will be missed. Particularly common sites for the lodging of emboli are in vessels of the spleen, kidney, brain and skin.

Heart Murmur

It has been estimated that a heart murmur is present sooner or later in 99% of patients (1, 11). The presence of some sort of murmur is thus the most regular accompaniment of the disease, and the diagnosis is rarely thought of in its absence. However, a few cases have been described in which, despite proved vegetations at autopsy, no murmur was ever heard during life. This is an exceedingly rare situation, but it is not so unusual to encounter cases in which no murmur can be heard early in the course, and the diagnosis is made only after several weeks of unexplained fever when a murmur appears. This may occur with vegetations on a bicuspid aortic valve which has been silent at first but which develops incompetence as the valve becomes eroded or with pyogenic infections implanted on a previously normal valve.

In three cases in the authors' experience the diagnosis of acute bacterial endocarditis has been made in retrospect in patients treated for bacterial pneumonia and cured, who several weeks later developed an aortic diastolic murmur. In these patients it appears that there was an unsuspected bacterial implant present during the pneumonia, that antibacterial therapy directed at the pulmonary infection also cured the endocarditis but that, in healing, sufficient scarring of the valve occurred to produce a murmur only after the active process of infection had subsided.

Although a cardiac murmur will almost invariably be found, it frequently is unimpressive and can be mistaken for

a functional one, the commonest being an apical systolic murmur associated with slight mitral insufficiency.

In many texts the finding of *changing* heart murmurs has been stressed as an important diagnostic criterion in bacterial endocarditis. With the exception of the appearance of an aortic diastolic murmur, as emphasized by Kerr (1), this sign is of little value, especially in the early phases of the disease. The interpretation of changes in the quality of murmurs is difficult at best since factors such as heart rate, cardiac output and blood viscosity as related to hematocrit determinations all may contribute. Most patients with the usual variety of bacterial endocarditis do not show striking changes in the murmurs beyond the physiologic variations noted. Exceptions, of course, are those with an infection causing unusually destructive lesions, as in pneumococcal endocarditis, leading to such sudden events as rupture of cusps, chordae tendineae or papillary muscles. These accidents generally produce unmistakable signs. There is nothing about the heart murmur per se in bacterial endocarditis which sets it apart from murmurs of other causes, and the interpretation of auscultatory findings must, as always, be made in the light of the total clinical picture.

Fever

Some degree of fever is present sooner or later in virtually every case of bacterial endocarditis, and quite properly one hesitates to make the diagnosis in its absence. Nevertheless, it must be appreciated that the occurrence of afebrile periods of as long as a few weeks or, rarely, several months may occur during the active course of the disease. Conversely, low grade fever *often* persists for variable periods after the institution of adequate antibiotic therapy.

The magnitude of fever is extremely variable from patient to patient and from time to time in the same individual but, in general, it tends to be higher in infections caused by pyogenic organisms and also in any patient at times when major embolic phenomena are occurring. Fever is most likely to be low grade or absent in the late stages of some infections when

a high degree of immunity to the infecting organism has been acquired and particularly in those cases manifesting severe renal involvement with nitrogen retention. Chills, chilly sensations and night sweats are common accompaniments of fever in this infection but are by no means universal.

One of the most frequent errors made in the management of bacterial endocarditis is to rely on the temperature chart as a guide to therapy without proper consideration of other factors. The point to be emphasized is that inadequate suppressive antibiotic administration will often bring the temperature to normal quite promptly but, on the other hand, optimal treatment is not invariably followed by complete absence of fever. Particularly in patients receiving large doses of penicillin and streptomycin intramuscularly for protracted periods, persistence of low grade fever for several weeks after eradication of the infection is extremely common. Presumably this is caused in many cases by the tissue reaction at the sites of injection of the antibiotics.

Embolic Phenomena

General.—There is disagreement as to the precise pathogenesis of some of the lesions here alluded to as embolic in origin, and it may well be that a number of the vascular lesions encountered in bacterial endocarditis are caused in part by allergic or other mechanisms. This point will be recognized but not discussed in detail for lack of definitive information to settle the issue and for lack of space. In any event, vascular damage of various sorts with blood vessel occlusion and/or rupture occurs frequently in this disease—sooner or later in all untreated cases. Of great practical importance is the fact that such lesions are not always recognized clinically and may be completely prevented with early initiation of therapy since they tend to occur relatively late in the course of the disease.

It is clearly impossible within the limits of this discussion to describe in detail all of the varieties of clinical findings associated with embolization which may involve any medium-sized or small artery in the body. Only certain of the

commoner pictures having diagnostic, prognostic or special therapeutic implications will be selected for consideration.

VASCULAR LESIONS OF SKIN.—Petechiae, or punctate hemorrhagic lesions of the skin or mucous membranes, have long been considered to be one of the characteristic findings in this disease. They occur ultimately in from one half to three quarters of untreated cases, occasionally are the first manifestation of the illness but usually are relatively late in appearing (1). They are not pathognomonic of any one underlying disease, of course, since they occur in many bleeding tendencies and in any disorder which causes small-vessel damage of sufficient magnitude. Furthermore, in otherwise normal people petechiae may be produced by excessive pressure changes such as those occasioned by strong sucking (in the buccal mucosa or soft palate) or by excessive coughing, straining or retching, in which cases petechiae of the conjunctiva or skin of the face may be seen. Nevertheless, a careful search for petechiae, splinter hemorrhages under the nails and hemorrhages in the eyegrounds is important in any case of suspected bacterial endocarditis, and the finding of such lesions adds weight to that diagnostic possibility.

Osler's nodes are described in the older literature not only as common (incidence as high as 50%), but also as being pathognomonic of bacterial endocarditis. Since they usually are a late manifestation, they are not frequently seen nowadays and, in addition, the same lesions are occasionally associated with other diseases (1). The node named for and first described by Osler is a small (pea-sized or less) tender, painful swelling of the pad of a finger or toe which lasts from several hours to a few days and may or may not show hemorrhagic discoloration. On the basis of biopsy studies, its embolic nature is in doubt, but the lesions when found are highly characteristic and are almost always indicative of bacterial endocarditis. The larger, slightly elevated, painless hemorrhagic areas in the skin of the palms or soles, termed "Janeway lesions," are also seen occasionally and are highly suggestive of the disease.

VASCULAR LESIONS OF VISCERA.—The spleen is more frequently the site of emboli than any other internal organ, and

a palpable spleen occurs in at least 50% of well-established cases during life (1). Infarction of the spleen causes pain in the left flank or left upper quadrant which is usually, but not invariably, sudden in onset and persists for several days. It is often confused with pleuritic pain and with lesions in the left lower lobe of the lung; since respiration usually accentuates it, there is sometimes an associated friction rub, and there may even be x-ray evidence of consolidation or fluid at the left base as a result of diaphragmatic involvement.

The kidneys are also frequently the site of emboli, both microscopic and, less often, large emboli which produce acute clinical symptoms and gross infarction. The latter when occurring on the left side may be confused with embolic phenomena in the spleen but the presence of hematuria will usually serve to distinguish the renal lesion.

Frank infarction of the intestine is unusual, but many patients are seen who have transitory abdominal pain suggesting ischemia of the bowel when the presumption is that emboli have lodged there but have not produced sufficient damage to the blood supply to cause necrosis.

EXTREMITIES.—Emboli to major arteries of the extremities occur, but not frequently. When they do, the findings are characteristic and obvious. Almost invariably conservative management suffices, and collateral circulation proves sufficient to maintain viability of the limb, although symptoms of low grade arterial insufficiency may be permanent sequelae, especially in older patients.

MYCOTIC ANEURYSMS.—These constitute an infrequent but serious complication of bacterial endocarditis. Their location is varied, any vessel being subject to involvement. Those occurring in abdominal, thoracic or cranial vessels are rarely detected until they rupture terminally, at which time little can be done. On the other hand, mycotic aneurysms of peripheral arteries are amenable to surgical treatment and should be looked for in all patients suspected of having bacterial endocarditis. The first symptom is usually relentless pain at the site of the aneurysm, this being followed by the appearance of a pulsating mass, local inflammatory swelling and tenderness and, in some cases, thrombosis of the involved vessel as well.

Even though the endocarditis may be cured bacteriologically, and the same may be true of the infection in the arterial wall, the aneurysm may be expected nevertheless to continue to enlarge under conservative therapy. The threat of rupture and continued disability make surgical excision with re-establishment of arterial continuity by means of a graft the procedure of choice whenever possible.

CEREBRAL VASCULAR LESIONS.—In addition to mycotic aneurysms of the cranial vessels which nearly always terminate in subarachnoid hemorrhage, one also encounters all too frequently central nervous system damage of varying degrees attributable to embolization of cerebral vessels followed either by hemorrhage into brain substance or by vascular thrombosis with ischemic necrosis of brain tissue. In infections caused by pyogenic organisms such as the staphylococcus, this process may extend further to abscess formation. These central nervous system complications are one of the most dreaded features of the disease, because damage once done cannot be repaired. Many of the emboli, however, are small and produce minor symptoms which are not incapacitating. Fortunately, spread of infection in the central nervous system or meninges rarely occurs.

EMBOLI TO THE LUNGS.—Patients with bacterial endocarditis in the left heart may, of course, like anyone chronically ill, have pulmonary emboli originating in phlebothrombosis of leg veins. It is not a frequent complication however. Contrariwise, if the vegetations are in the right heart or are on a left to right shunt, emboli from vegetations will lodge in the pulmonary circuit. Several special features of this situation deserve comment. In the first place, such patients are usually thought to have repeated bouts of pneumonia for some time before the true diagnosis is made. Also, the diagnosis may be especially difficult because bacteremia may be absent for long periods or at least be unusually difficult to demonstrate. The emboli are not large enough to block the major pulmonary arteries and cause sudden death, but infected infarcts may give rise to pulmonary suppuration if antibiotic therapy is not adequate.

Cardiac Manifestations

Subacute bacterial endocarditis of the common variety caused by non-hemolytic streptococci is but rarely engrafted on normal heart valves (see Pathogenesis, p. 13). It is somewhat surprising, therefore, that cardiac symptoms, especially those of congestive failure, are uncommon in the early phases of the disease. In fact, even in untreated cases before the antibiotic era, approximately half ran their full course without the development of failure. On the other hand, cardiac failure is now the commonest cause of death in treated patients and is one of the poorest prognostic signs (1, 11). Usually its appearance during or after antibiotic treatment indicates such severe valvular and myocardial damage that the outlook for prolonged survival, even though the infection may be cured, is not good. A few patients who decompensate during the active disease go on to excellent recovery and live at least ten years after, but they are distinct exceptions to the general rule. It is clear, nevertheless, that with reversal of factors contributing to failure, such as active myocarditis and increased demand on the heart because of fever, sepsis and anemia, compensation may be regained in some instances.

Those patients whose aortic valves are badly damaged are most likely to develop intractable failure. Tight mitral stenosis is relatively uncommon in bacterial endocarditis despite the high incidence of underlying rheumatic valvular damage. It is perhaps partly because of this that the incidence of auricular fibrillation preceding bacterial endocarditis is also low. More often than not, neither the patient nor his physician will have his attention particularly focused on the heart by the symptomatology early in the disease.

The incidence of concomitant active rheumatic fever is difficult to establish. So many features of the two diseases overlap, notably fever, joint pains, heart murmur, anemia, myocardial changes and so forth, that it is often difficult clinically to distinguish one in the presence of the other. Most of the evidence from antistreptolysin O studies, together with autopsy data, indicate that coexistence of the two diseases does occur, but is relatively uncommon, certainly in less than 10% of cases of bacterial endocarditis.

Clubbing of the Fingers

Despite the fact that the fundamental cause of clubbing is unknown, it is a useful clinical sign in a number of conditions if the finding is interpreted with caution and the existence of congenital clubbing is recognized. The sign is particularly helpful in distinguishing bacterial endocarditis from rheumatic fever, which at times may be a real problem. Clubbing is not associated with uncomplicated rheumatic fever or with old rheumatic heart disease. It does develop commonly in bacterial endocarditis but usually not until the second or third month of the disease. Extreme degrees of pulmonary osteoarthropathy are rarely found, but early clubbing, as evidenced by edema and looseness of the nail beds with a loss of the normal angulation, should be looked for as an extremely helpful clinical sign.

Renal Damage

As already noted (see Pathology, p. 16), some degree of involvement of the kidneys by one or more of several processes is common in well-established bacterial endocarditis. In the earliest phases of the infection there may be no clinical evidence of renal damage, but before long microscopic hematuria with or without albuminuria can be found at least intermittently in the great majority of cases. At the other end of the spectrum, some patients present with renal insufficiency as the most prominent feature and may be thought to have glomerulonephritis or pyelonephritis as the primary disease. This situation is particularly apt to occur in older patients and in those in whom the course is relatively indolent. Fever may not be at all prominent, and organisms may be difficult or impossible to culture from the blood, thus compounding the difficulties in the way of diagnosis. The process here is, of course, a diffuse nephritis, the precise pathogenesis of which is unknown, but clinically, as far as the renal abnormalities are concerned, it is often indistinguishable from chronic glomerulonephritis.

Laboratory Tests

Other than the finding of positive blood cultures which is discussed under Bacteriology (p. 5) and Diagnosis (below), there are several helpful guides from the laboratory. Abnormalities in the urine have already been mentioned. Hematologic findings are variable, but a mild to moderate normocytic normochromic anemia is almost always found in the well-established disease, unless there was a pre-existing polycythemia due to cyanotic congenital heart disease. The white blood count is most often normal except after major embolic accidents or in patients with infections due to pyogenic organisms, when a striking leukocytosis may be found. An increase in the number of monocytes as well as the finding of large phagocytic cells presumed to be reticuloendothelial in origin has been described by several observers (1).

No specific serologic or skin tests have been demonstrated to be of value in the diagnosis of bacterial endocarditis. However, some elevation of the gamma globulin fraction is almost always found, and this is reflected in abnormalities in non-specific liver function tests such as the cephalin-cholesterol flocculation and thymol turbidity tests which are usually positive in this disease without necessarily connoting any serious degree of liver damage. An increase in the sedimentation rate as well as C-reactive protein is the rule in bacterial endocarditis, except in the earliest stages, and cryoglobulins have also been found in a number of patients.

Skin and muscle biopsy may be done in occasional cases because of suspected polyarteritis nodosa or allied diffuse vascular disease. In this connection it is of interest that we were recently misled by the interpretation of such a specimen as showing lesions consistent with "hypersensitivity angiitis" in a patient who was later proved at autopsy to have had bacterial endocarditis.

DIAGNOSIS

The urgent need for early and accurate bacteriologic diagnosis in bacterial endocarditis cannot be emphasized too

strongly. The first step in accomplishing this end is maintenance of a high index of suspicion in any patient with a heart murmur which might be organic. Whenever such a patient is not well for a week or more or presents with unexplained anemia, renal damage or hemiplegia, blood cultures should be taken even though fever may not be prominent. If the patient has recently had a tooth extracted or has had urinary tract manipulation, one should be even more suspicious. When fever is present for more than a week in conjunction with one or more of the above findings without some other cause being found, one should take a series of blood cultures and start treatment promptly without waiting for the results. We believe the same course should be followed in any patient with valvular heart disease and unexplained fever of over a week's duration, even in the absence of an obvious cause for bacteremia, if he shows any corroborative signs such as petechiae, clubbing, splenomegaly, microscopic hematuria or other embolic lesions.

In other words, whenever the working clinical diagnosis is bacterial endocarditis, it is wise to collect a series of four to six blood cultures, taken at intervals of an hour or so, and then to start treatment promptly with a view to modifying it later in the light of the bacteriologic findings. One is not justified in withholding therapy until the results of cultures are known when the presumptive diagnosis is a disease as serious and at times as rapidly progressive as this. On the other hand, identification of the infecting organism is also highly desirable. With this fact in mind, it is important to balance the risks in every case. For example, one might wait a few days before starting therapy in the case of a patient who has already been administered antibiotics which might interfere with the obtaining of positive cultures from the blood. This latter decision must be made in the light of the patient's clinical condition. If it is too precarious and if he has already had such heavy antibiotic therapy that the likelihood of getting positive cultures seems remote, one may be forced to continue treatment blindly for fear of losing the patient while trying to make the diagnosis. Conversely, there are times when a patient has had a great deal of antibiotic

treatment without the bacteriologic diagnosis ever having been established, and is not doing well in spite of what should be adequate therapy. Under these circumstances it may be wise to stop treatment altogether and take repeated blood cultures in the hope of recovering the organism and then being able to design a more rational course of antibiotic administration. The choice of such alternatives must be a highly individualized matter and depends on many factors which require careful analysis.

Other difficult decisions arise in the case of patients who clinically are judged probably *not* to have bacterial endocarditis but in whom the possibility exists and cannot reasonably be ruled out. For instance, some patients present findings which could be attributed to rheumatic activity, disseminated lupus erythematosus or subacute bacterial endocarditis. If after careful study with lupus erythematosus preparations, blood cultures and so forth, no definite diagnosis is established, one may be obliged to treat the patient for bacterial endocarditis, even though he feels it is probably not the correct diagnosis, on the grounds that such a course offers the patient the only definitive therapeutic chance, small though it may be.

It is fully recognized that in following the plan outlined above, a number of patients will be treated for bacterial endocarditis who do not have the disease, but this is necessary in the same way that a good surgeon must expect to remove some normal appendices or some benign gastric ulcers which clinically might have been malignant.

Fortunately, the difficult diagnostic problems which have been stressed here do not make up the bulk of cases encountered. In between 70 and 90% of cases, positive blood cultures can be obtained, thus clinching the diagnosis (1). A few points in regard to blood cultures deserve emphasis. The finding of non-hemolytic streptococci without other organisms in a blood culture cannot be attributed readily to contamination. Bacteremia with this organism occurs sufficiently infrequently as a transitory episode in otherwise normal people that, while one cannot accept a single positive culture as unequivocal proof of bacterial endocarditis, it must be taken

seriously if the rest of the clinical evidence is compatible. The finding of two or more blood cultures positive for nonhemolytic streptococci means bacterial endocarditis until proved otherwise.

Staphylococcus albus presents grave difficulties because it is frequently found as a contaminant in blood cultures, but it also is increasingly important as a cause of bacterial endocarditis. Hence, the finding of this organism in a culture of blood must be interpreted with great caution, but it cannot be disregarded. Usually, further cultures and careful clinical observation will settle the issue satisfactorily.

Blood cultures should be incubated for at least three weeks before being discarded as negative since some organisms, particularly those which have been exposed to sublethal amounts of antibiotics, are slow to grow out. Close co-operation and, whenever possible, verbal consultation between the physician and the bacteriologist responsible for cultures and antibiotic sensitivity tests are strongly urged as essential to the proper management of these patients.

TREATMENT

General

Despite the fact that penicillin has been available for almost 15 years and is conceded to be the most effective agent in most cases of endocarditis, there is still no uniformity of opinion concerning the optimal therapy of this infection. Particularly controversial are questions related to the form of the drug to use, the route of administration, the duration of therapy, the desirability of using combinations of antibiotics and so forth. Beeson (21) has recently summarized the problem of optimal duration of therapy is an excellent editorial. As each new antibiotic comes on the market, its role in the treatment of bacterial endocarditis needs to be evaluated. Some guiding principles are needed to steer one through the maze of antibiotics and laboratory data to a sensible plan of treatment for the patient at hand.

The first point on which there might be agreement is that the earliest possible complete eradication of the bacteria in the vegetations is desirable if not essential. The second point is that no one regimen will take care of all cases. Treatment must be varied from patient to patient, depending especially on the nature of the infecting organism. Third, and of great importance, this cannot be done simply by treating the patient with the antibiotic to which his organism is most "sensitive" by in vitro tests (see Antibiotic Sensitivity Tests, p. 9). Overwhelming clinical experience has shown that some antibiotics which have looked very promising, as judged by their ability to inhibit organisms in vitro, have all too often done no more than suppress the infection in the patient despite prolonged and heavy therapy. This has been true of all of the tetracycline antibiotics and also of chloramphenicol and erythromycin in streptococcal endocarditis. The probable explanation for this apparent discrepancy is that the action of these antibiotics against most strains of non-hemolytic streptococci is predominantly bacteriostatic. Strong evidence has been presented in detail elsewhere that the successful treatment of bacterial endocarditis usually requires *a bactericidal effect from the antibiotics used, and certainly this should be the basic aim of therapy* (8, 9, 10).

It is fully recognized that a sharp distinction cannot be drawn between bacteriostatic and bactericidal effects in many cases, and it is also true that some antibiotics or combinations of drugs may be bacteriostatic for one organism and bactericidal for another. Nevertheless, some generalizations may be made which have some validity.

The broad spectrum antibiotics of the tetracycline series and chloramphenicol are rarely bactericidal when used alone. The combination of one of these agents with streptomycin is in some circumstances bactericidal. Penicillin has primarily a bactericidal action for organisms against which it is active. An important exception is the enterococcus, against which optimal concentrations of penicillin are only partially lethal, and in this instance the addition of streptomycin to penicillin will usually bring about total killing of the bacterial popula-

tion, even though by itself streptomycin is quite ineffective (see Antibiotic Sensitivity Tests, p. 9). Streptomycin, bacitracin and polymyxin usually have a bactericidal effect on bacteria against which they are active. Erythromycin and carbomycin fall in an intermediate position in that their effects are quite variable but often incompletely bactericidal.

The evaluation of combinations of antibiotics is extremely complex and cannot be dealt with in detail here. Jawetz (22) has studied this subject extensively both in vitro and in certain animal infections. Some combinations were found to be synergistic, others indifferent or additive and still others antagonistic. Antagonism was found particularly between the broad-spectrum antibiotics and penicillin, in which case the early lethal effect of penicillin was interfered with. The clinical importance of this antagonistic action is probably not great in most infections since conditions as to concentration of the antibiotics, timing, size of the bacterial population and so forth have to be rather narrowly adjusted in order to demonstrate it in animals. Also there is little evidence from experience with patients that antibiotic antagonism has led to poor therapeutic results. One exception is the report of Lepper and Dowling (23) concerning pneumococcal meningitis treated with penicillin and aureomycin. Nevertheless, in an infection as serious as bacterial endocarditis in which prevention of relapse by total elimination of bacteria from the lesions is particularly desirable, the avoidance of combinations of antibiotics known to exhibit antagonism at times would appear to be wise except when other evidence outweighs this theoretic consideration.

In contrast, synergism between antibiotics has been observed to occur in the treatment of several infections, notably in bacterial endocarditis. The synergistic effect of penicillin-streptomycin combinations against enterococci and some strains of viridans streptococci has already been discussed (see Antibiotic Sensitivity Tests, p. 9), and this synergism has been clearly demonstrated in the treatment of non-hemolytic streptococcal endocarditis in patients.

Treatment of Endocarditis Caused by Penicillin-Sensitive Streptococci

Infections caused by streptococci which are inhibited in vitro by 0.1 unit/ml. or less of penicillin are designated as penicillin sensitive, and they can usually be cured by penicillin alone given on a variety of schedules. Generally recommended have been courses of 2 million units or more per day parenterally for four weeks. The use of oral penicillin is not recommended because of the difficulties attending the large dosage which would be required and the uncertainty of absorption.

Hamburger and Stein (24) have reported considerable success with a two-week course of intensive parenteral penicillin, but others (11, 25) have found that courses as short as two weeks with penicillin alone were attended by a high relapse rate. No series has been extensive enough to be decisive, and a few relapses have occurred in all series of sufficient magnitude to be significant, no matter what the regimen.

Because of the striking synergistic effect of penicillin and streptomycin against enterococci and some strains of viridans streptococci (see Antibiotic Sensitivity Tests, p. 9), it was suggested by Hunter (8), after favorable results in a few cases, that a short (about two weeks) course of penicillin plus streptomycin might prove satisfactory in penicillin-sensitive infections and would thus appreciably reduce the period of hospitalization, cost and inconvenience to the patient. It also seemed possible that the relapse rate might be reduced still further on this regimen. Published results of such therapy have been favorable, but the number of patients reported has been relatively small (26, 27, 28). A number of investigators have been loath to cut the course of treatment to two weeks under any circumstances and have felt that the possible gain was not "worth the risk." The question really becomes, "Is the 'risk' real or fancied?"

In order to try to shed light on this problem the authors have gathered the published as well as the unpublished experience of 23 investigators in this regard in the hope that the combined experiences might provide some form of definitive

answer.* A total of 146 patients with penicillin-sensitive streptococcal infections received a course of combined penicillin-streptomycin therapy lasting approximately two weeks. Ten of these 146 strains were sensitive to 0.25 = 0.5 unit/ml. of penicillin; the remainder were sensitive to 0.1 unit/ml. or less. The dose of penicillin ranged from about 2 to 12 million units daily and streptomycin or dihydrostreptomycin was given in amounts of approximately 2 Gm. daily. Of these, only eight patients could possibly be considered as having had a bacteriologic relapse either on clinical grounds or because of recurrence of positive blood cultures, giving a treatment failure or relapse rate of 6%. This figure compares favorably with those available for longer periods of therapy and appears to support the continued use of a short-term (two weeks) penicillin-streptomycin regimen *in the case of penicillin-sensitive streptococcal endocarditis.*

Although most viridans streptococci are sensitive to penicillin (inhibited by 0.1 unit/ml. or less), occasional strains are encountered which require from 0.2 to 2.0 units/ml. and which may be classified as intermediate between the usual sensitive varieties and the resistant enterococci. The management of infections caused by these organisms should probably be the same as that recommended for enterococcal endocarditis despite the fact that cures have been reported with less rigorous regimens. Short-term treatment cannot be recommended for this group at present.

Treatment of Endocarditis Caused by Enterococci

As mentioned previously, enterococcal infections are of increasing frequency and importance in recent years. The management of these infections differs so drastically from that of the usual infection with penicillin-sensitive viridans

*The authors gratefully acknowledge the co-operation of the following investigators: Wright Adams, Paul B. Beeson, A. I. Braude, Paul A. Bunn, Harry F. Dowling, Maxwell Finland, Charles K. Friedberg, J. E. Geraci, Count D. Gibson, Jr., Morton Hamburger, Carl G. Harford, L. E. January, Chester S. Keefer, William M. M. Kirby, Yale Kneeland, Jr., Vernon Knight, Max Michael, Jr., Lowell A. Rantz, Charles H. Rammelkamp, Wesley W. Spink, William S. Tillett, Ralph Tompsett and Theodore E. Woodward.

streptococci that the recognition of enterococcal infections is of critical import and deserves special emphasis (see Bacteriology, p. 5). Treatment with penicillin alone, even in large doses, cures but a small proportion of these infections. Likewise, treatment with the antibiotic to which the organism is most sensitive by routine in vitro tests (usually one of the broad-spectrum antibiotics) is most often unsatisfactory. The striking in vitro synergistic effect of penicillin and streptomycin against almost all strains of enterococci (see Antibiotic Sensitivity Tests, p. 9) has been amply confirmed by clinical experience in patients (29, 30). One other feature sets enterococcal infections apart from the usual streptococcal endocarditis, namely their persistence and, hence, the unequivocal need for more prolonged therapy. Accordingly, the recommended course of treatment is at least 10 million units of crystalline penicillin daily combined with streptomycin in doses of 1 to 2 Gm. a day for six weeks. The penicillin is best given every three to four hours intramuscularly and may be administered with 1% procaine in order to minimize pain. The optimal dosage of streptomycin is less well defined, but it is advisable to start with 2 Gm. a day in two divided doses at 12-hour intervals and to consider reducing the dose to 1 Gm. daily after two to four weeks if signs of toxicity appear. Such a regimen is admittedly rigorous, both in terms of discomfort to the patient and of hazards of streptomycin toxicity, but these drawbacks seem relatively minor in view of the otherwise fatal nature of the disease. The sites of injection in the buttocks invariably become exceedingly tender, indurated and inflamed but, in our experience, no serious consequences or permanent sequelae have resulted, except for damage to the vestibular branch of the eighth nerve in a few patients.

In the occasional patient in whom this regimen fails, one may try greatly increased doses of penicillin (up to 120 million units per day) or penicillin combined with bacitracin, each of which has been successful in a few refractory cases. Benemid® in such instances may also be considered. Experience to date indicates that the broad-spectrum antibiotics should only be tried in enterococcal endocarditis as a last

resort and after failure with the above mentioned regimens. Allergic reactions to penicillin are *not* a contraindication to continuing the drug unless they appear to be life-endangering. Except in most unusual circumstances, reactions of this sort can be minimized by the administration of antihistaminics or, if necessary, cortisone and, in our experience, it has never been necessary to discontinue penicillin in a patient who needed it as a lifesaving measure.

Treatment of Endocarditis Caused by Staphylococci

The increasing frequency of antibiotic-resistant strains of staphylococci and the increasing importance of this organism as a cause of endocarditis have already been alluded to (see Bacteriology, p. 5). The therapy of staphylococcal infections is complicated by many factors, notably the great variation different strains exhibit with respect to antibiotic sensitivity, the difficulty of sterilizing lesions with any agent or combination of agents and the extensive valve damage which staphylococci can produce in a relatively short time. Some general principles can be offered as a guide to therapy although it should be emphasized that every staphylococcal infection should be approached as a separate problem.

No single antibiotic can be safely relied on in the treatment of staphylococcal endocarditis, and at present two or more drugs in combination are required for treatment. Although a bactericidal drug combination should still be the aim, this unfortunately cannot be realized in many cases. It should be stressed repeatedly that each staphylococcus should be tested in vitro for its sensitivity to a variety of antibiotics, including penicillin, streptomycin, erythromycin, chloramphenicol and at least one of the tetracycline agents. This procedure will give some general idea of the antibiotic sensitivity pattern of the particular strain in question and frequently provides a rational basis for altering therapy later on if indicated by the clinical course.

Penicillin in amounts of 10 million units daily plus full doses of erythromycin, chloramphenicol, or both should be

started immediately if staphylococcal endocarditis is a good diagnostic possibility, or if this diagnosis is confirmed by preliminary blood culture findings. One cannot wait for the results of in vitro antibiotic sensitivity tests before instituting therapy in view of the serious and frequently rapid course this type of infection may assume. If the strain is found to be penicillin sensitive and the clinical response appears satisfactory over the first few days and subsequent blood cultures remain sterile, this drug combination can be continued.

Unfortunately, in anywhere from 40 to 70% of instances, the strain will turn out to be penicillin resistant. In such cases the organism will usually be sensitive to erythromycin and/or chloramphenicol or inhibited by bacitracin on the basis of in vitro studies. This situation probably reflects the less extensive use these antibiotics have had in the general population in recent years. It has been our practice to continue large amounts of penicillin, even though the organism proves to be penicillin resistant in vitro, for the following theoretic reason: penicillin-resistant strains of staphylococci encountered clinically invariably produce penicillinase, an enzyme which inactivates penicillin. In the presence of massive amounts of this drug, the penicillinase produced by these organisms could theoretically be tied up and the staphylococci thereby rendered susceptible to the action of penicillin. If the clinical response to this regimen is unfavorable, bacitracin or one of the tetracycline antibiotics may be added. Streptomycin combined with penicillin has not been shown to exert an appreciable synergistic effect on staphylococci, and the benefit from streptomycin in this type of situation is difficult to assess but is apparently not great. If the well-known agents fail, one is justified in resorting to a number of relatively untested or potentially toxic newer antibiotics which may be available. We have been impressed with the fact that erythromycin and chloramphenicol appeared to be the most important drugs employed in several cases of serious penicillin-resistant staphylococcal infections from which patients have recovered under our observation in recent months.

Because of the notorious capacity of staphylococci to cause abscesses in various organs and the great propensity of this

organism to persist in such lesions, even despite antibiotics, relapse is always a threat, and it is probably wise to treat patients for extended periods. The proper antibiotic program, once arrived at by in vitro studies and clinical observations, should be continued for at least two weeks after all evidence of infection has subsided, as judged by clinical and laboratory data. Evidence of local suppurative processes such as arthritis, empyema or lung abscesses should be looked for constantly since they usually demand surgical drainage.

PROPHYLAXIS

Theoretically it would be possible to prevent bacterial endocarditis altogether if one were able to eliminate the occurrence of bacteremia. Unfortunately this appears to be a practical impossibility since transitory bacteremia may often be asymptomatic and occurs under many circumstances which do not bring the patient to a physician. However, the organisms most commonly responsible for endocarditis are known to invade the blood stream frequently in association with a variety of procedures, notably tooth extraction, tonsillectomy and urinary tract manipulation (see Pathogenesis, p. 13). Thus, in certain selected circumstances the prophylactic use of an antibacterial agent in patients with known or suspected valvular heart disease appears warranted. Such prophylaxis would be aimed to (1) prevent bacteremia, (2) reduce its magnitude should it occur and (3) eliminate bacteria implanted on heart valves before a vegetation is formed.

Sulfonamides have proved completely unsatisfactory in this connection. These drugs have not significantly reduced the incidence of bacteremia after tooth extraction, and a number of cases of bacterial endocarditis have occurred after tooth extraction despite full doses of sulfa drugs. This has been explained by the relatively feeble action of sulfonamides against the non-hemolytic streptococci, together with the fact that these drugs are bacteriostatic rather than bactericidal in their action against micro-organisms.

Penicillin has been shown to decrease bacteremia associated with certain events. Glaser and his associates (31) dem-

onstrated that penicillin significantly reduced the incidence of bacteremia following dental extraction, particularly in association with infected gums. However, they still recovered organisms from 43% of patients five minutes or less after the dental procedure despite 50,000 units of penicillin given intramuscularly every two hours day and night for 24 hours before extraction. Similar data have been furnished by other workers. Rhoads, Sibley and Billings (32) have recently reported that the incidence of post-tonsillectomy bacteremia was significantly decreased when 600,000 to 800,000 units of penicillin were given daily for at least four days prior to operation but not when penicillin was administered for only 24 hours prior to operation. It should be noted that in the study of Glaser and his group and in essentially all of those carried out subsequently, penicillinase was added to the blood cultures immediately. A somewhat artificial situation was thereby created, and some organisms may have been permitted to survive and grow out in the blood cultures which would have been killed had they remained in contact with penicillin in the patient. Evidence that penicillin can fail to exert its desired and anticipated prophylactic role has been provided by a few reports of endocarditis due to viridans streptococci which has occurred after dental extractions despite penicillin prophylaxis. It is accepted that penicillin alone cannot be expected to alter bacteremia due to penicillin-resistant organisms, particularly enterococci, which is prone to occur with procedures on the genitourinary and intestinal tract. In such situations prophylaxis with combined penicillin-streptomycin would theoretically be most likely to prevent bacteremia and decrease the hazard of resulting endocarditis. The value of penicillin-streptomycin in minimizing bacteremia associated with prostatectomy is under investigation in several clinics, but data are not yet available to indicate the efficacy of this type of program.

Roth and his co-workers (33) have investigated the use of broad-spectrum antibiotics for prophylaxis and reported the reduction of positive blood cultures from 56% in untreated patients after tooth extraction to 2% in patients receiving aureomycin. Similar results with chloramphenicol have been

reported by Pressman and Bender (34). Although these studies are encouraging, one must bear in mind that aureomycin and the other broad-spectrum antibiotics are primarily bacteriostatic agents and cannot be counted on to eradicate organisms from an early focus on a heart valve. Clinical experience with such agents in the prophylaxis of endocarditis is still meager. At present, one is forced to conclude that their value in this regard remains to be established, but their further study is warranted.

One of the major difficulties in evaluating any prophylactic program is occasioned by the fact that bacterial endocarditis has been estimated to occur in only one of approximately 500 patients with known valvular heart disease subjected to a single dental extraction. It is apparent that a tremendous clinical trial with careful controls would be necessary before dogmatic statements about any regimen could be made. No such data are available and, in their absence, one is forced to make recommendations on insufficient evidence and based largely on theoretic considerations.

The importance of pretreatment for several days before tooth extraction is unknown. It seems improbable that with any form of antibiotic therapy one would be able to sterilize periapical abscesses. If one attempted to do so by prolonged pretreatment, it is conceivable that the originally sensitive populations of microorganisms would be replaced by antibiotic-resistant ones so that, at the time of tooth extraction, sterilization of the blood stream would be less feasible than without pretreatment.

The unpleasant fact emerges that one has no satisfactory answer to prophylaxis as yet. Therefore, the following statements are offered only as a guide:

1. Sulfonamides are almost certainly inadequate in the prophylaxis of bacterial endocarditis.

2. Broad-spectrum antibiotics may be of value, but their position has not been established clearly.

3. Penicillin by itself appears to be the most effective agent against most strains of non-hemolytic streptococci, which are the greatest offenders, and even though penicillin administered in doses of 1 to 2 million units a day, preceding

tooth extraction by a few hours and continued for 48 hours after, does not completely eliminate bacteremia, it is probable that in most instances organisms reaching the heart valve are killed in situ before a vegetation can be formed.

4. Penicillin in amounts of 1 to 2 million units a day should probably be given for at least four days before and two days after tonsillectomy and other procedures on the upper respiratory tract where grossly infected areas are encountered.

5. It seems reasonable that penicillin alone will not provide adequate protection for situations involving the genitourinary and intestinal tracts where enterococci and gram-negative organisms may be anticipated. In these instances, combined penicillin and streptomycin should probably be employed.

PROGNOSIS

Although the average cure rate for bacterial endocarditis in general stands around 70% at present, many factors materially influence the chance for cure in individual patients. Some of the most important of these include the type of infecting organism, the site of bacterial implantation, the extent of pre-existing heart damage and the duration of disease prior to treatment. Staphylococcal endocarditis is still a highly lethal condition with a cure rate averaging only about 50% in most centers. In contrast, streptococcal endocarditis may be expected to result in a cure in anywhere from 75% to more than 90% of patients, depending on whether enterococci or penicillin-sensitive streptococci, respectively, are the causative agents. The prognosis is less favorable if the aortic valve is the seat of vegetations or if the state of pre-existing cardiac compensation is precarious. The appearance of heart failure during the course of the disease is always an ominous sign and is of serious prognostic import. Heart failure, renal decompensation and embolic accidents account for most of the deaths other than those caused by uncontrolled infection and, since these complications characteristically occur relatively late in this disease, early diagnosis and early treatment cannot be too strongly urged.

Relapses are encountered most commonly within two weeks after termination of therapy and are uncommon after one month. They do not necessarily indicate that cure is impossible, but rather call for more intensive and heroic measures which in many cases eventually result in eradication of the infection.

More and more reports clearly indicate that patients not only can be cured of their infection but can subsequently go on to enjoy an active and productive life for many years.

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